December 23, 1999

NDA 21-156
NDA 20-998/S-007

G. D. Searle & Co.
Attention: Anita Piergiovanni, M.Sc.
Director, Worldwide Regulatory Affairs
4901 Searle Parkway
Skokie, IL 60077

Dear Ms. Piergiovanni:

Please refer to your new drug application (NDA) dated June 24, 1999, received June 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Celebrex (celecoxib) capsules.

We acknowledge receipt of your submissions dated July 28, August 19, October 6, November 9, 10, 30, and December 2, 3, 8, 16, 17 and 23, 1999. The user fee goal date for this application is December 25, 1999.

Please also refer to the December 23, 1999, supplemental new drug application NDA 20-998/S-007.

The new drug application provides for Celebrex to reduce the number of adenomatous colorectal polyps in Familial Adenomatous Polyposis patients, as an adjunct to usual care.

Supplemental NDA 20-998/S-007 and NDA 21-156 provide for identical changes to the CLINICAL PHARMACOLOGY, CLINICAL STUDIES, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the currently approved labeling.

We have completed the review of this application, as amended, and the supplemental new drug application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the application (NDA 21-156) and the supplemental application (NDA 20-998/S-007) are approved under 21 CFR Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

All supplements and other submissions should be addressed to the original NDA 20-998 for this drug product, not to this NDA 21-156, except for the 20 copies of final printed labeling and advertising material as noted below.

The final printed labeling (FPL) must be identical to the enclosed labeling text. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-156 and NDA 20-998/S007." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing studies (Subpart H Phase 4 commitments) specified in your submission dated December 23, 1999. These commitments, along with any completion dates agreed upon, are listed below.

1. A randomized controlled trial in familial adenomatous polyposis (FAP) that will verify and describe the clinical benefit of Celebrex in this population. Your proposal for a placebo-controlled study of adolescents with FAP aged 12 to 19 years who are genotypically positive but phenotypically negative is acceptable. This study should be completed and results submitted to FDA with due diligence.

2. A long-term registry of clinical outcomes in FAP patients. Your proposal for enrolling patients aged 12 years or above to Celebrex 400 mg BID is acceptable. Eligible patients would include those who are phenotypically positive who a) have not had primary prophylactic surgery, b) have not had secondary surgery, or c) have had both primary and secondary surgery. Time to FAP-related events (FAP-related surgery, gastrointestinal cancer, desmoids, or death) and adverse events will be collected and compared to untreated historical controls. Information collected on registry patients should be submitted to the NDA on an annual basis.

Final study reports should be submitted to NDA 20-998 as supplemental applications. For administrative purposes, all submissions relating to these Phase 4 commitments must be clearly designated "Subpart H Phase 4 Commitments."

In addition, we note your following Phase 4 commitments, specified in your submission dated December 23, 1999, that are not a condition of the accelerated approval. These commitments, along with any completion dates agreed upon, include:

1. A randomized controlled trial in sporadic adenomatous polyps. Your proposal for

a placebo-controlled study evaluating the proportion of patients with new adenomas at year 1 and year 3 is generally acceptable. Additional comments regarding the length of patient follow-up will be forthcoming.

2. For patients on Study 001, submission of data on the number of polypectomies performed, the size and histology of polyps removed, including diagnosis of malignancy, for each treatment arm. Correlation of polypectomy findings with the observed reduction in polyp counts should be made for each arm

3. For patients on Study 001, submission of biomarker data for each treatment arm (e.g., crypt morphology and apoptotic index, p53 expression, COX messenger RNA/protein expression, etc). Correlation of biomarker findings with the observed reduction in polyp counts should be made for each arm

4. For patients on Study 001, submission of data on dietary habits at baseline and on study, for each treatment arm. If imbalances across arms are noted, an analysis of the impact of dietary factors on polyp reduction should be performed.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for use of Celebrex in pediatric patients with phenotypically positive FAP, but we recognize that you will be conducting a study in pediatric patients who are FAP gene carriers who have not expressed the FAP phenotype.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Paul Zimmerman, Project Manager, at (301) 594-5775.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure